Informed Consent in Genomic Research: The Iterative Feedback Model

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Informed Consent in Genomic Research: The Iterative Feedback Model

August 14, 2015

Felicitas Holzer, M.Sc.
Content

• **Introduction**

• Justification of the iterative feedback model

• Development of the iterative feedback model
Sequencing Technologies and the 1000 $ Genome


IMBS Symposium: Science, Ethics and Society
Genome Wide Association Studies

• Subtype of human health research using WGS/WES procedures
• Association of large number of genetic variants with phenotypic traits

Some challenges of genome-wide data collection in research

- Obligations towards third parties
- Confidentiality and data protection
- Storing, sharing and distributing genomic information
- Disclosure of incidental findings
**Definition**

“[...] a finding concerning *health or reproductive importance* and is discovered in the course of conducting research but is *beyond the aims of the study*. This means that IFs [Incidental Findings] may be on variables not directly under study and may not be anticipated in the research protocol.” (Wolf et al. 2008, Eckstein et al. 2014)
Specific aim

To present a new *informed consent model* for the *disclosure of incidental findings* to potential individual research participants in human health research study using whole genomic sequencing (*WGS*)/whole exome sequencing (*WES*) (*genomic*) procedures.
The iterative feedback model complies with ethical principles better than alternative models given the specific characteristics of genomic data

- Holzer, F., Mastroleo, I. (2014): “Does the pragmatic model undermine the importance of the ethical obligations involved in information process? A defence of continuous genetic counselling for research participants.” Journal of Medical Ethics (eLetter)

Content

• Introduction

• Justification of the iterative feedback model

• Development of the iterative feedback model
General structure of the argument

Strategies for the ethical justification of the iterative feedback model

1. Specifying the informed consent requirement
2. Analysing characteristics of genomic data
3. Evaluating informed consent models based on ethical principles
   - Commonly found ethical principles in literature
   - Comparison of exemplary consent models extracted from literature review and interviews
1. The informed consent (IC) requirement

According to the *standard ethical informed consent requirement* (Eyal 2011), an informed consent model should grant

(1) full transmission of all relevant information

(2) full comprehension of all relevant information

(3) voluntariness
1. Characteristics of genomic data

Characteristics of genomic data

- Heterogeneity
- Irreversibility
- Connectedness
- Uncertainty

Consequences for the return of results (ROR)

- Predictability
- Reach
- Privacy
<table>
<thead>
<tr>
<th>Informed consent requirement</th>
<th>Corresponding characteristics of WGS/WES data, ROR</th>
</tr>
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<tbody>
<tr>
<td><strong>(1) Full transmission of all relevant information</strong>&lt;br&gt;- Information important and relevant to participant and relatives&lt;br&gt;- Delicate and individual information needs an extended consent process</td>
<td>Connectedness, Privacy, Reach&lt;br&gt;Irreversibility, Heterogeneity, Predictability</td>
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<td><strong>(2) Full comprehension of all relevant information</strong>&lt;br&gt;- Assurance that participants are fully aware of consequences linked to WGS/WES data; impact on psychological health&lt;br&gt;- Difficulty to predict if findings contribute to benefits and harms of participant</td>
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<td><strong>(3) Voluntariness</strong>&lt;br&gt;- Voluntary consenting on study participation</td>
<td>Personal and delicate information (privacy)</td>
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3. Ethical principles (1-3)

- **Autonomy** (Beauchamp and Childress 2009)/**Respect for Persons** (Belmont Report, National Commission 1979)
- **Beneficence/Non-Maleficence** (Beauchamp and Childress 2009)
- **Justice** (Beauchamp and Childress 2009)
- **Intellectual Freedom and Responsibility** (Presidential Commission 2013)
- **Practicality** (Appelbaum et al. 2014)
3. Ethical principles (2-3)

- Autonomy/Respect for Persons
- Practicality
- Beneficence/Non-maleficence
- Intellectual Freedom and Responsibility
- Justice
Can practicality override autonomy?

In most of the consent models, the criterion of practicality has overshadowed the ethical demand of respect for persons.

Models of Consent to Return of Incidental Findings in Genomic Research

BY

PAUL S. APPELBAUM, ERIK PAREN, CAMERON R. WALOMAN, R. KLITZMAN, ABBY FYER, JOSUE MARTINEZ, W. NICHOLSON PRICE, WENDY K. CHUNG

Support for Full Disclosure Up Front

Investigators who conduct whole genome sequencing presumably should inform subjects that there may be findings that lie beyond the primary aims of the research but might be very important to the subject. But how should they tell them about that possibility, and how should the findings be explained?
3. Ethical principles (3-3)

Conclusion: Ethical evaluation of informed consent models

Taking into account the evaluation of prototypic informed consent models (Appelbaum 2014), I argue for

- Extensive information transmission prior to research participation (autonomy)
- Researchers are responsible to return results (ROR) (justice, intellectual freedom and responsibility)
- Extensive counselling aiming for minimization foreseeable harm, maximize possible benefit (Beneficence/Non-maleficence)
General argument

- Full transmission of relevant information
- Voluntariness
- Full comprehension
- Characteristics of genomic data and ROR
- Autonomy + other ethical principles
Content

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Relying on a continuous counselling process

The dynamic consent model

Data Subjects can change their consent preferences

- Data Subjects are Notified and kept informed of where and when their data was used.
- Data Controllers Use and Share your data, restricted by the Data Subject's consent.

The iterative model

- based on dynamic consent model
- complemented by a guided and continuous counselling process

(Centre for Health, Law and Emerging Technologies (HeLEX), University of Oxford, London School of Economics and Political Science, HW Communications Ltd)
Which findings should be disclosed?

The “3V” framework (Eckstein et al. 2014)

Validity: Scientifically valid findings

Value: “[...] a normative property regarding the worth, significance, or utility of a research finding (whether subjective or objective)”

Volition: Participants’ preferences

Figure 1: The “3V” Framework for Analyzing the Ethics of Disclosing Secondary Findings. As a threshold requirement to fall within the scope of a disclosure framework, information must constitute a “research finding.” To meet the substantive requirements to qualify for disclosure, research findings must meet the requisite requirements of validity, value, and volition.
Crucial steps in the informed consent process – the iterative feedback model

- Interview
  - Disclosure of IF; “3V” framework
  - New counselling unit
  - Transfer of relevant information
  - Opportunity to ask questions
  - Informed consent form
  - Summary research results (new counselling unit)
Disclosure of Incidental Findings fulfilling the “3V”

Data Base 2
- Known Associations (Literature, Data Bases, Data Banks)

Data Base 1
- Individual Genome (Genome Data Base of research study)

Data Base 3
- New Discoveries (Literature, Data banks)

Step 1: check once in Data Base 1 and 2 for relevant findings in individual Genomes

Step 2: check repetitively in Data Base 1 and 3 for relevant variants in individual Genomes

Inform participant
Why does an “iterative” model comply with the ethical informed consent requirement for research projects using WGS/WES procedures?

Characteristics of WGS/WES data

- Predictability/Uncertainty
  - genotype-phenotype associations that are not yet known but at a future point in time
- Heterogeneity
  - information can be easily overlooked; iterative communication process aims for information transmission that is as complete as possible
- Connectedness
  - e.g. preferences concerning reproductive decisions can arise later in the course of the research conduct
Why does an “iterative” model comply with the ethical informed consent requirement for research projects using WGS/WES procedures?

**Autonomy**
- Participants’ preferences can change over time

**Information disclosure and comprehension**
- Information transmission and comprehension improve if embedded in an iterative process
"The new iterative feedback model complies with ethical principles better than alternative models given the specific characteristics of WGS/WES data" (Hypothesis)
Acknowledgement

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Prof. Judith Fischer, Freiburg

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IMBS Teams in Buenos Aires and Freiburg
Thank you
Muchas gracias
Danke
धन्यवाद
SUPPLEMENT
## 1. Characteristics of genomic data (3-3)

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Communication Process between researcher and counsellor

**Data Base 2**
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**Step 2:** check repetitively in Data Base 1 and 3 for relevant variants in individual Genomes

*Inform participant*
“3 agents approach”

- Researcher
- Counsellor
- Participant

Exchange of results, participant's preferences

Responsibility of researchers towards participants, validity, value, volition

Information disclosure via counselling, ROR, consent taking

IMBS Thesis Defense 2015
Resource consumption even years after the study conduct (counselling obligations prior to, during and after trial)

Is the iterative feedback model cost-effective?

Cost-effectiveness (Cost-benefit-analysis)

• Measures health interventions in a representative monetary value

• Compares outcomes (e.g. life years gained, deaths avoided) with costs
(1) Practicality (2-2)

- Can we estimate costs/benefits prior to research conduct?
- Should former health care costs be taken into consideration?
- Funding obligations by other agents than researchers
- Supportive tools (e.g. Software tools for screening of data bases, data banks; automated communication processes)
Which findings should be disclosed? (1-2)

- **Primary** findings researchers deliberately seek for
- **Anticipatable** findings associated with the test procedure
- **Anticipatable** findings recommended to seek for by expert commission
- **Unanticipatable** findings, not known to be associated with the test procedure

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<tr>
<th>TYPE OF RESULT DISCOVERED</th>
<th>DESCRIPTION</th>
<th>EXAMPLE</th>
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<tr>
<td>Primary Finding</td>
<td>Practitioner aims to discover A, and result is relevant to A</td>
<td>In a child with unknown vaccine history, a test done to determine a child's immunity status before the chickenpox vaccine is administered</td>
</tr>
<tr>
<td>Incidental Finding: Anticipatable</td>
<td>Practitioner aims to discover A, but learns B, a result known to be associated with the test or procedure at the time it takes place</td>
<td>Discovering misattributed paternity when assessing a living kidney donor and potential recipient who believe they are biologically related</td>
</tr>
<tr>
<td>Incidental Finding: Unanticipatable</td>
<td>Practitioner aims to discover A, but learns C, a result not known to be associated with the test or procedure at the time it takes place</td>
<td>When a DTC genetic testing company identifies a health risk based on a newly discovered genetic association not knowable at the time a previous sample was submitted</td>
</tr>
<tr>
<td>Secondary Finding</td>
<td>Practitioner aims to discover A, and also actively seeks D per expert recommendation</td>
<td>ACMG recommends that laboratories conducting large-scale genetic sequencing for any clinical purpose should look for variants underlying 24 phenotypic traits</td>
</tr>
<tr>
<td>Discovery Finding</td>
<td>Practitioner aims to discover A through Z by employing a test or procedure designed to detect a broad array of results</td>
<td>A “wellness scan,” a whole body computed tomography (CT) scan, is intended to discover any abnormal finding throughout the body</td>
</tr>
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</table>

Source: Presidential Commission 2013: 27
Ancillary care (Richardson and Belsky 2004) is defined as

- “Care not required by sound science, safe trial conduct, morally optional promises, or redressing subject injury”
- Therapeutic consequences, if there are treatment options or preventive measures, resulting from the disclosure of findings
(3) Ancillary care obligations (2-2)

Future work should address (cf. Merritt 2011)

- If there are ancillary care obligations (referring to general principles)
- If yes, for which type of findings are they mandatory
- Lower and upper limits of the extension of the obligations (should be non-arbitrarily located)
The rare diseases genomes project, U.K.

- 3 years project, started in 2013
- Pilot project for Genomics England (Aim: to sequence 100,000 genomes in total)
- Sequencation of 10,000 genomes of individuals with rare genetic diseases
- Supported by University of Cambridge, Genomics England and Illumina

- GWAS (Genome Wide Association Study)
  - Subtype of human health research using WGS/WES procedures
  - Association of large number of genetic variants with phenotypic traits

Source: University of Cambridge, Research.
http://www.cam.ac.uk/research/news/
## 2. Ethical principles (2-3)

My ethical analysis of to prototypic models (Appelbaum et al. 2014)

<table>
<thead>
<tr>
<th>Model</th>
<th>Autonomy</th>
<th>Beneficence/Non-maleficene</th>
<th>Justice</th>
<th>Intellectual freedom/responsibility</th>
<th>Practicality</th>
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<td>Traditional consent model</td>
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<tr>
<td>Staged consent model</td>
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<td>Mandatory return model</td>
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<tr>
<td>Outsourcing model</td>
<td>Depending on counselling service</td>
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Direct-to-Consumer Tests

Companies offering genetic screening for several features

- intelligence, aptitudes, monogenetically caused diseases etc.
- Risk factors and optimization of drug therapies
- Incidental findings only partially reported (ACMG)

Source: www.23andme.com (2013)
Polymerase Chain Reaction

Figure 2: Schematic drawing of the PCR cycle. (1) Denaturing at 94-96°C. (2) Annealing at (eg) 68°C. (3) Elongation at 72°C (P=Polymerase). (4) The first cycle is complete. The two resulting DNA strands make up the template DNA for the next cycle, thus doubling the amount of DNA duplicated for each new cycle.

Source: serc.carleton.edu (2013)